AMERICAN JOURNAL OF PHYSICAL ANTHROPOLOGY 106:47–60 (1998)

Clues to Recognition of Fungal Origin of Lytic Skeletal Lesions

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KEY WORDS blastomycosis; pathology; lytic lesion, bones

ABSTRACT The present study addresses the specificity of lytic osseous impact for distinguishing among metastatic cancer, tuberculosis, and fungal disease. *Osseous impact* is used in this manuscript as a convention to describe the macroscopic appearance of defleshed bones affected by the disease.

Osseous changes in the skeleton of a 47-year-old black male, diagnosed in life as having blastomycosis, were characterized and compared to lytic lesions observed in ten individuals with tuberculosis and six with metastatic cancer in the Terry and Hamman-Todd Collections.

Apparent distinguishing characteristics are identified. Eroded areas, present as fronts of resorption or the result of space-occupying masses in blastomycosis, with protruding, short, blunt, 1×2 mm spicules of new bone, are surrounded by periosteal reaction. These differed from smooth zones of resorption and coalesced lesions, with a smoothed marginal zone and space-occupied appearance—bone-displacing mass—in tuberculosis and lytic (non-permeative) lesions of metastatic cancer. *Displacing* is a convention (an artificial term) denoting bone resorption and reformation at the outer edge of the tumor mass, giving the impression that the surrounding bone had expanded beyond its original margins. Irregular trabeculae are occasionally preserved in the margins, but remodeling in the form of blunting of those trabeculae is not observed macroscopically in either tuberculosis or metastatic cancer.

Two apparently specific lesion types are noted in blastomycosis. Periosteal reaction surrounding fronts of resorption appears specific, at least for nonarticular osseous lytic lesions, among the three entities studied. Remodeling of isolated internal trabeculae in the space-occupying mass lesions of blastomycosis also appears unique among the three disorders studied. Comparison with coccidioidomycosis suggests that extrapolation of blastomycosis findings to other fungal diseases is feasible; description of additional clinically diagnosed cases is awaited. Am J Phys Anthropol 106:47–60, 1998.

Granulomatous disease of bone, such as tuberculosis and fungal diseases, has long been of interest in paleopathology (Buikstra, 1976; Ortner and Putschar, 1981; Steinbock, 1976). Among such granulomatous diseases

Contract grant sponsor: National Museum of Natural History, Smithsonian Institution.

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Received 20 June 1996; accepted 18 January 1998.

is blastomycosis, a fungal disorder caused by *Blastomycosis dermatitidis* (Body et al., 1988; Gehweiler et al., 1970). One of the rare paleopathologic documentations of this phenomenon is the report of Allison et al. (1979), describing mummified soft tissue. Blastomycosis is rarely suggested as a diagnosis in the paleopathology literature (Ortner and Putschar, 1981; Zimmerman and Kelley, 1982). Other reports on it (Buikstra, 1976; Kelley and Eisenberg, 1987) are based on presumed osseous impact. *Osseous impact* is used in this paper to describe the macroscopic appearance of defleshed bones affected by the disease.

The actual macroscopic osseous impact of clinically documented blastomycosis has not yet been characterized, except for the indirect perspective provided by radiologic, intraoperative (surgical), and microscopic examination (Baily et al., 1991; Barrack et al., 1983; Bayer et al., 1979; Carnesale and Stegman, 1956; Chick, 1971; Colonna and Gucker, 1944; Gehweiler et al., 1970; Jones and Martin, 1941; Kalbhen, 1991; MacDonald et al., 1990; Resnick and Niwayama, 1988; Rhangos and Chick, 1964).

While skeletal patterns of some diseases have proven to be diagnostic at the population level (Ortner and Putschar, 1981; Rothschild and Rothschild, 1995a; Rothschild and Woods, 1990; Zimmerman and Kelley, 1982), isolated elements usually do not lend themselves to similar discrimination. The various treponemal diseases, erosive arthritides, and granulomatous diseases usually cannot be distinguished on the basis of examination of isolated elements (Kelley and Eisenberg, 1987; Ortner and Putschar, 1981; Rothschild and Martin, 1993). There are exceptions, however.

Advances in understanding of pathological processes and careful observation of defleshed bones with confirmed clinical diagnosis provide new diagnostic opportunities for application to archeologic specimens. We feel it is critical to distinguish between speculative and data-based analysis. As the life history of most archeologically derived skeletons is not usually available, information derived from clinically diagnosed cases has the potential to transform speculation into sound, data-based diagnosis. One such example is gout. Fronts of resorption, which describe erosions in rheumatoid arthritis and spondyloarthropathy (after Leisen et al., 1987; Rothschild and Woods, 1991) are sufficiently different in appearance from the space-occupying mass appearance of gout to allow the latter to be recognized even if only an isolated bone is available.

Confident diagnosis of skeletal disease in the archeological record is dependent upon anticipated skeletal impact. While one can speculate on how a given disease might affect bone (Steinbock, 1976), interpretations based on untested assumptions can be misleading (Rothschild, 1992; Rothschild and Martin, 1993; Rothschild and Rothschild, 1995a; Zias, 1996). Documentation of the actual osseous changes in individuals with well-established clinical diagnosis would allow confidence in that diagnosis, especially if the osseous impact of other diagnostic considerations (differential diagnosis) is also similarly documented. The present study used the latter approach to investigate the value of examination of individual lytic lesions to allow metastatic cancer, tuberculosis, and fungal disease to be distinguished. Thus, specificity speculations attributed to Ortner and Putschar (1981), Steinbock (1976), and Buikstra (1981) on this matter could be examined. Although tuberculosis and metastatic cancer have been well described in the paleopathological literature (Brothwell and Sandison, 1967; Buikstra, 1981; El-Najjar, 1981; Ortner and Putschar, 1981; Steinbock, 1976), the osseous impact of fungal disease has been only occasionally illustrated (Ortner and Putschar, 1981; Zimmerman and Kelley, 1982). The latter is herein addressed through detailed description of the osseous lesions of clinically diagnosed blastomycosis and its radiologic correlation (Harrison et al., 1991; Resnick and Niwayama, 1988). These are then contrasted with those caused by tuberculosis and metastatic cancer.

MATERIALS AND METHODS

The complete skeleton of a 47-year-old black male, diagnosed in life as having blastomycosis, was examined at the National

TABLE 1. Skeletal distribution (percentage affected) of granulomatous osteomyelitis[1] and cancer[2]

	1 Blasto-T	2 Blasto-L	3 Coccl-d	4 Crypto-c	5 Sporo-T	6 Tuberc	7 Echino-c	8 Brucella	9 Cancer
Lower limb									
Femur	−	3	0	5	3	3–12	13	0	27
Tibia	+	10–12	8	9	30	12	10	0	3
Fibula	−	3–4	0	0	6	0	0	0	0
Tarsal	−	7	19	0	0	0	0	0	0
Metatarsal	−	6–7	19	1	3	0	0	0	0
Phalange (feet)	−	1	0	0	12	4–6	0	0	0
Upper limb									
Humerus	+	2–6	4	9	0	3	3	0	9
Radius/Ulna	−	4–9	4	6	6	0	0	0	3
Carpal/Metacarpal	−	8–9	4	0	21	2	0	0	0
Phalange (hand)	−	1–2	4	0	3	3	0	0	0
Axial skeleton									
Vertebrae	+	11–15	23	27	0	74	37	58	12
Ribs	+	11–15	0	13	3	11–41	10	0	15
Clavicle	−	1–2	8	6	0	3	0	0	3
Sternum	+	5	0	1	0	29	0	0	0
Scapula	+	1	0	0	0	0	7	0	6
Innominate	+	3–7	4	16	3	6–12	20	0	91
Mandible	−	0–2	0	0	0	0	0	0	?
Skull	+	3–13	0	10	1–6	0	0	6	

[1]Derived from Jones and Martin (1941), Colonna and Gucker (1944), Steinbach (1966), Altner and Turner (1970), Gehweiler et al. (1970), Waldvogel et al. (1970), Nicholson (1974), Chleboun and Nada (1977), Bjorksten and Boquist (1980), El-Najjar (1981), Bried and Galgiani (1986), Torricelli et al. (1990), and de Dios Colmenero et al. (1991).
[2]1, blastomycosis—Todd; 2, blastomycosis—literature; 3, coccidioides; 4, cryptococcus; 5, sporotrichosis; 6, tuberculosis; 7, echinococcus; 8, brucella; 9, cancer.

Museum of Natural History, Smithsonian Institution, in Washington, D.C. The affected skeleton (T-833R) is from the Terry Collection, which consists mainly of late nineteenth century–early twentieth century white and black individuals from the St. Louis, Missouri, area. Macroscopic examination of the skeleton was performed noting changes in skull, long bones, vertebrae, and ribs. A ×10 magnifying glass was also used to examine lytic lesions.

Lytic lesions in ten additional individuals diagnosed during life with tuberculosis and six diagnosed with metastatic cancer were identified in the Terry Collection and the Hamman-Todd Collection (Cleveland Museum of Natural History). These were examined to characterize the lytic lesions and identify distinguishing characteristics.

Radiographs were obtained of the entire skeletons with bones in the normal anatomic position.

The Hamman-Todd and Terry Collections were specifically selected because they represent individuals who were diagnosed in life but who lived prior to the availability of effective treatment. The diagnostic applicability of these cases to archeological populations/samples seems reasonable, as these disorders have not been amenable to treatment until very recent times.

RESULTS

Findings in blastomycosis

Skeletal alterations are predominantly lytic in nature (Tables 1, 2). The initial perspective is that the lesions in T-833R are different in character than those observed in skeletons with clinically documented tuberculosis or cancer (Table 3). The major bony changes observed are described below from a regional perspective.

Skull. A round 10 × 10 mm defect, with well-defined margins, is present on the left parietal bone, 2 cm from the sagittal suture and 1 cm from the coronal suture (Fig. 1). Two surrounding circumferential zones are noted on the ectocranial aspect. The most proximate ectocranial zone consists of unevenly distributed pits and remodeled fronts of resorption. The latter are largely superficial, only focally penetrating the ectocranial plate. Blunt spicules (1 × 2 mm) of new bone project from the fronts of resorption. This proximate zone is surrounded by a second zone of slight periosteal reaction. The total

TABLE 2. Demographics and character of granulomatous infections[1] and cancer[2]

	Blas	Histo	Cocci	Crypt	Spor	Cand	TB	Bruce	Echin	Eosin	Canc
Geography											
Midwest	++	++									+
Southeast	++			+	+				+		+
Southwest		+	++	+						+	
West									+		+
Appalachians		+									+
Mexico			++	+							+
Central America	Rare		++	+							+
South America	Rare		+	+					+		+
Characteristics											
Frequency (%)	14–16	<1	0.5–1	5–10	<1	<1	5–20	25	1–2	10–50	
Multiple	+		+	+			+	+		+	+
Moth-eaten	Rare	+									+
Lytic margins											
Punched out	+			+						+	−
Well-defined	+		+	+						+	−
Sclerotic	+			+/−					+		+/−
Resorptive pr.											
Sacroiliac							Rare	++	+		+
Vertebrae endplate	++[3]		+				++	++[4]		+	+/−
Bony prominance	+		+	+							
Hand/foot diaphyses	+		+								
Others											
Diaphyseal thick		+	+/−				+				
Joint predominant							+				
Cortical expansion			+						+		
Periosteal reaction	50%		30%					+	+	+	

[1]Derived from Carter (1934), Altner and Turner (1970), Dalinka and Greendyke (1971), Buikstra (1976), Drutz and Catanzaro (1978) Bayer and Guze (1979), Bayer et al. (1979), Goodwin et al. (1980, 1981), Barrack et al. (1983), Bried and Galgiani (1986), MacDonald et al. (1990), Torricelli et al. (1990), de Dios Colmenero et al. (1991), Kalbhen (1991), and Rao et al. (1991).
[2]Blas, blastomycosis; Histo, histoplasmosis; cocci, coccidiomycosis; Crypt, cryptococcus; Spor, sporotrichosis; Cand, candidiasis; TB, tubercellosis; Bruce, brucellosis; Echin, echinococcus; Canc, cancer. +/−, rare occurrence; +, occasional occurrence; ++, common occurrence.
[3]Centrum, with late involvement of arch or ribs.
[4]Without periosteal reaction.

TABLE 3. Distinguishing characteristics of lytic lesion in blastomycosis, tuberculosis and cancer

Lesion character	Blastomycosis	Tuberculosis	Cancer
Expansile	Present	Absent	Present
Fronts of resorption	Present	Absent	Present
Zones of resorption	Absent	Present	Absent
Trabecular remodeling	Minimal	Minimal	Absent
Smoothing/remodeling of subjacent trabeculae	Absent	Occurs	Absent
Equal dissolution of cortical and trabecular bone	Yes	No	No
Reactive surrounding bone	Slight	Very slight	Absent
Coalescence of lesions	Absent	Frequent	Occurs
Affects posterior vertebral elements	Yes	No	Yes

size of the lesion (defect and surrounding zones) is 22 × 24 mm.

The proximate endocranial aspect of the defect is surrounded by quasilinear bands of resorption that extend downward and laterally into the groove of the main branch of the middle meningeal artery (Fig. 2). Slight periosteal reaction (2 mm in width) forms a discontinuous external surrounding zone. The dimensions of the affected endocranial region are 25 × 20 mm. Radiological evaluation reveals a 1 cm lytic lesion with well-defined borders, interrupted by isolated internal projections (Fig. 3). Irregular, "moth-eaten" resorption is present adjacent to the lytic lesion.

Appendicular skeleton. A sharp, marginated, 7 × 5 mm lesion is present on the vertebral border of the scapula, surrounded by a circumferential belt of periosteal reaction (similar to that noted in the skull) (Fig. 4). Long bone lesions are asymmetrically distributed. Irregular periosteal bone deposi-

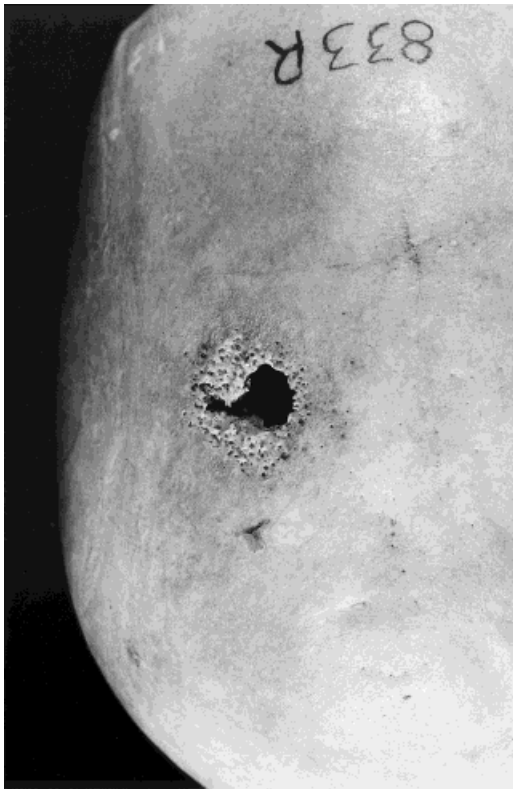

Fig. 1. Superior view of ectocranium of skull (Terry 833R). A round left parietal defect with well-defined margins is surrounded by two circumferential zones. The most proximate consisted of unevenly distributed pits and remodeled fronts of resorption. Blunt spicules of new bone protrude from the fronts of resorption. The proximate zone is surrounded by a second zone of slight periosteal reaction.

Fig. 2. Endocranial view of skull (Terry 833R). Quasi-linear bands of resorption surround the defect. Slight periosteal reaction forms a discontinuous external circumferential zone.

tion is present on the lateral epicondylar ridge of the humerus surrounding a 4 × 20 mm smoothly excavated region. The latter consists of two compartments: the distal compartment is totally smooth and elliptoid in shape, while the proximal compartment is composed of three contiguous 1–2 mm deep elliptical regions penetrated by minimal new bone. Linear periosteal reaction, at the distal third of the tibial diaphysis (Fig. 5), is associated with focal, marked serpentine rugosity.

Axial skeleton. Focal lytic areas with sharply defined margins are present in several cervical vertebrae. They have a space-occupying-lesion character, as if the excavated area had been occupied by a mass. The granulomatous tissue formed as a response to the blastomycotic infection is a space-occupying structure which leaves a recognizable negative imprint in the residual bone. Minimal reactive new bone is present. Lesions that are contiguous with vertebral end plates freely penetrated those end plates.

Irregular, well-defined, 15 × 20 mm zones of resorption are noted in several lumbar vertebrae (Fig. 6) and the sacrum. These areas have a space-occupying-lesion character. The lytic areas are surrounded by pitted zones and fine periosteal reaction (arrowhead) involving the superior lateral margins and pedicle. Periosteal reaction is generally restricted to the anterior aspect of the lower thoracic and upper lumbar vertebrae. Periosteal reaction is not limited to vertebrae with macroscopically observed lytic lesions.

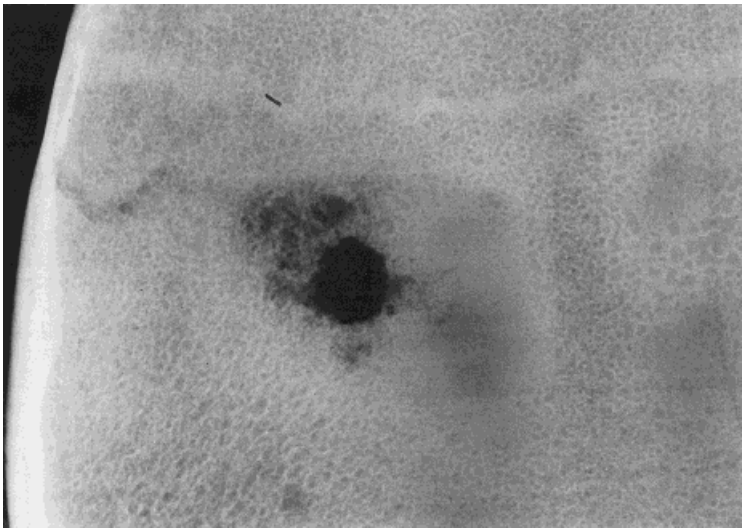

Fig. 3. Superior-inferior x-ray view of calvarium (Terry 833R) illustrated in Figs. 1 and 2. Lytic lesions with well-defined borders, interrupted by isolated internal projections. Irregular, moth-eaten resorption is present adjacent to the lytic lesion.

Large, irregular lytic areas are present in several ribs, extending to the costovertebral and costochondral junctions (Fig. 7). They are associated with minimal periosteal reaction. Reactive new bone is minimal, occasionally associated with an irregular, moth-eaten radiologic pattern (Fig. 8). A pathologic fracture is present in one rib, through such a lytic lesion. Mild marginal periosteal reaction is also noted on the sternum.

Characteristics of lytic lesions in tuberculosis

Individual lytic lesions in individuals with tuberculosis are characterized as excavations (Figs. 9, 10), with very slight reactive surrounding bone. The most characteristic aspect is observation of smooth zones of resorption, in contrast to the fronts of resorption noted with blastomycosis (Figs. 1, 2). The term *zones of resorption* describes a macroscopic regional phenomenon, whereas *fronts of resorption* describes a phenomenon recognizable only under 10× magnification. The latter is apparently caused by individual osteoclast-induced resorption. Internal trabeculae are occasionally spared in tuberculosis, with minimal remodeling (e.g., blunting) of those trabeculae. New bone formation is quite modest, even when de-

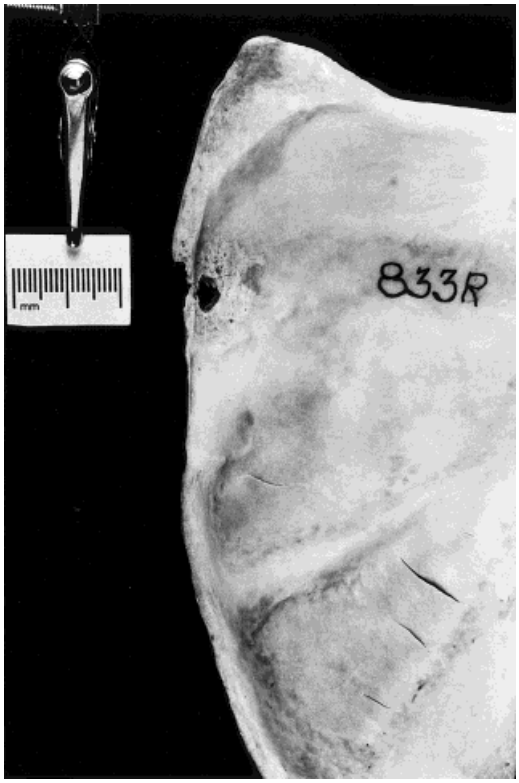

Fig. 4. Ventral view of medial aspect of scapula (Terry 833R). Sharp marginated lesion, surrounded by circumferential belt of periosteal reaction.

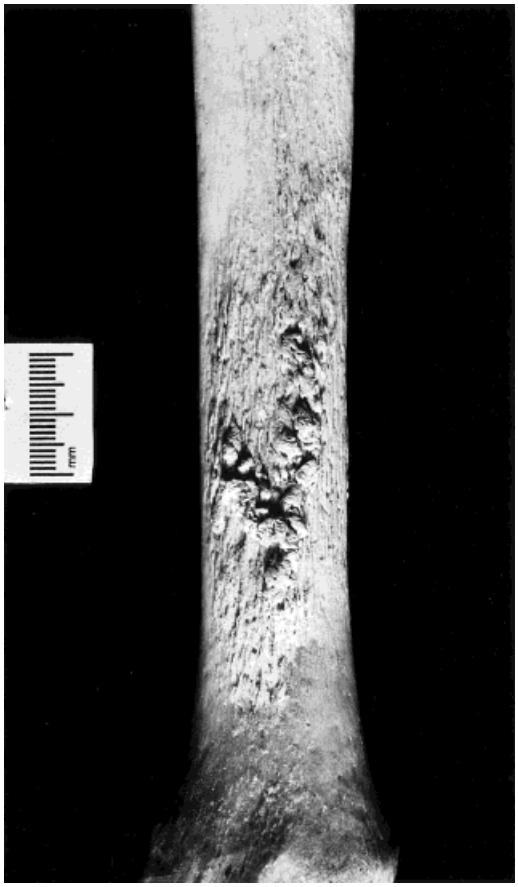

Fig. 5. Lateral aspect of tibia (Terry 833R). Periosteal reaction at the distal third of the tibial diaphysis associated with focal serpentine rugosity.

struction is so extensive as to produce the classic gibbus deformity (Fig. 11). Posterior vertebral elements are usually spared, with the exception of zygapophyseal joints.

Frequent coalescence of lesions in tuberculosis (Figs. 9, 10) contrasts with blastomycosis. The latter lesions tend to occur as isolated phenomena. In addition to granulomatous space-occupying lesions, draining abscesses are associated with new bone formation–induced smoothing of subjacent trabeculae (Fig. 12). Rather than simply being resorbed, the subjacent trabeculae are remodeled to produce a smooth surface of the exposed trabeculae. Appendicular lesions are often associated with reactive new bone formation and occasional fusion of adjacent bones.

Characteristics of lytic lesions in metastatic cancer

Two types of nonblastic lesions are noted in metastatic cancer: permeative and discrete lytic lesions. Permeative lesions are easily distinguished from the lytic areas characteristic of blastomycosis. *Permeable* refers to small pores or openings, typically requiring 10× magnification for visualization. Discrete lytic lesions in individuals with metastatic cancer have a space-occupying appearance resulting from the formation of an expansile bone displacing mass (Figs. 12, 13). *Displacing* is used here as a term to denote bone resorption and reformation at the outer edge of the tumor mass. Irregular trabeculae are occasionally preserved in the margins, but remodeling (e.g., blunting) of those trabeculae is not observed. Perilesional periosteal reaction is notably absent, in contrast to that associated with hypertrophic osteoarthropathy and unrelated to actual osseous infection. Lytic cancerous lesions are not associated with any evidence of cortical remodeling, while remodeling is invariably present in tubercular lesions. That remodeling is below the threshold for radiologic recognition. Thus, the cortical margins of cancerous lesions often breach a macroscopically unremodeled cortex. The process results in bone resorption without inducing formation of new, structural reinforcing bone. As trabecular bone is less dense than cortical bone, the latter is affected later in the disease course. The result is often a thin, residual, unremodeled cortical margin. Resorption of underlying trabecular bone results in an unsupported residual shell (Fig. 14).

DISCUSSION

The nature of the skeletal lesion(s) of blastomycosis is described. They present variably as fronts of resorption or the sequellae of space-occupying masses. Protrusions of blunt 1 × 2 mm spicules of new bone from the eroded areas and surrounding periosteal reaction seem ubiquitous, at least to the lesions in T-833R (Figs. 1–10). The lytic lesion in the skull of T-833R (Fig. 1) is unique and different in appearance from those of metastatic cancer and tuberculosis.

Fig. 6. Lateral aspect of lumbar vertebra (Terry 833R). Focal lytic area with sharply defined margin, as if excavated by a mass. Pitted zones and fine periosteal reaction are present at the superior lateral margin and pedicle.

Space-occupying lesions which spare isolated trabeculae are also noted in coccidoidomycosis and are often associated with a localized periosteal reaction (C. Merbs, personal communication). It is unclear if the tendency to preserve the outer cortex (even in expansile lesions), which is noted in coccidioidomycosis, represents either a true difference between the skeletal impact of the two fungal diseases or simply a biologic variation of the host reaction or pathogen. Studies of additional clinically documented cases of fungal disease will be required to determine the answer to that question.

Blastomycosis was first isolated from a human patient in 1897 (Selby, 1975). It is a dimorphic fungi, growing in filamentous form at room temperature and in yeast form at body temperature. Pathogenicity appears limited to the yeast form (Barrack et al., 1983). The characteristic single, broad-based bud recognized in the yeast form allows histologic identification of the organism. Blastomycosis causes sharply defined, eccentric metaphyseal and diploic lesions, as noted above (Gehweiler et al., 1970; MacDonald et al., 1990). Blastomycosis involves the bone in 14–60% of disseminated cases (Table 1) (Bayer et al., 1979; Kalbhen, 1991). It predominantly affects vertebral centra, with late involvement of neural arches and ribs (Kelley, 1989). Periosteal reaction is present in 50% of osseous cases. In addition to macroscopically visible lytic lesions, radiologic evaluation may reveal an irregular, moth-eaten pattern (Gehweiler et al., 1970), as also noted in T-833R. It is not known if the isolated long bone periosteal deposition with focal, marked serpentine rugosity is part of this process or if it represents cooccurrence of another, unidentified process.

While it is unknown if the character of the bone lesions seen in blastomycosis can be distinguished from other fungal diseases (i.e., histoplasmosis, coccidioidomycosis, cryptococcoses, blastomycosis, and candidiasis), at least the distribution pattern of skeletal lesions should prove helpful in distinguishing among them (See Tables 1 and 2 based on the following studies: Altner and

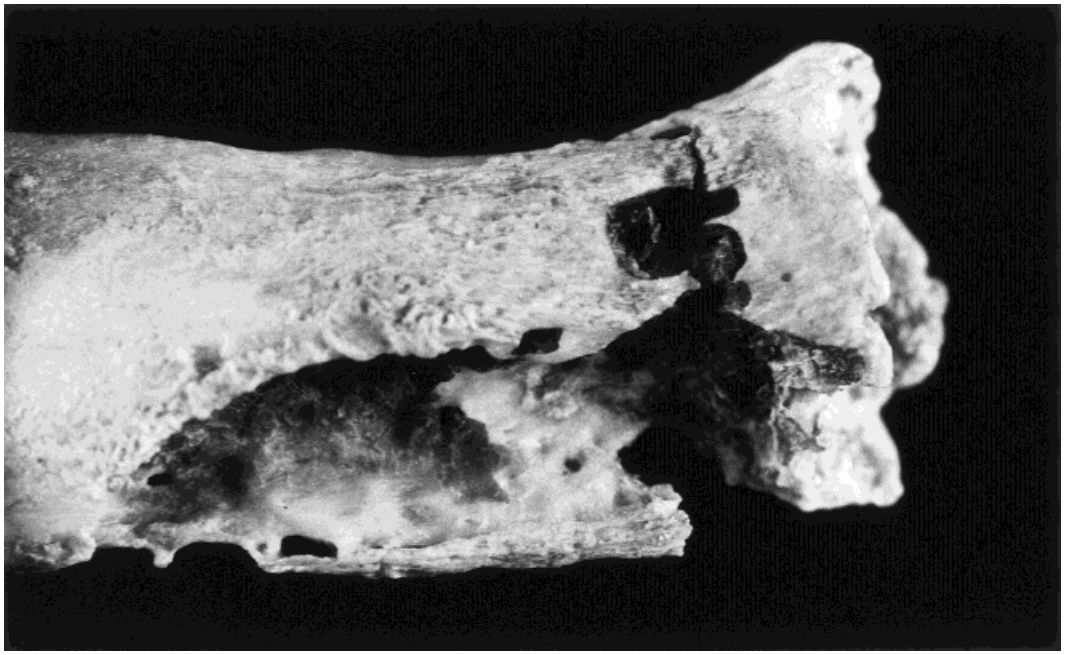

Fig. 7. External aspect of sternal end of rib (Terry 833R). Large, irregular lytic area with minimal periosteal reaction.

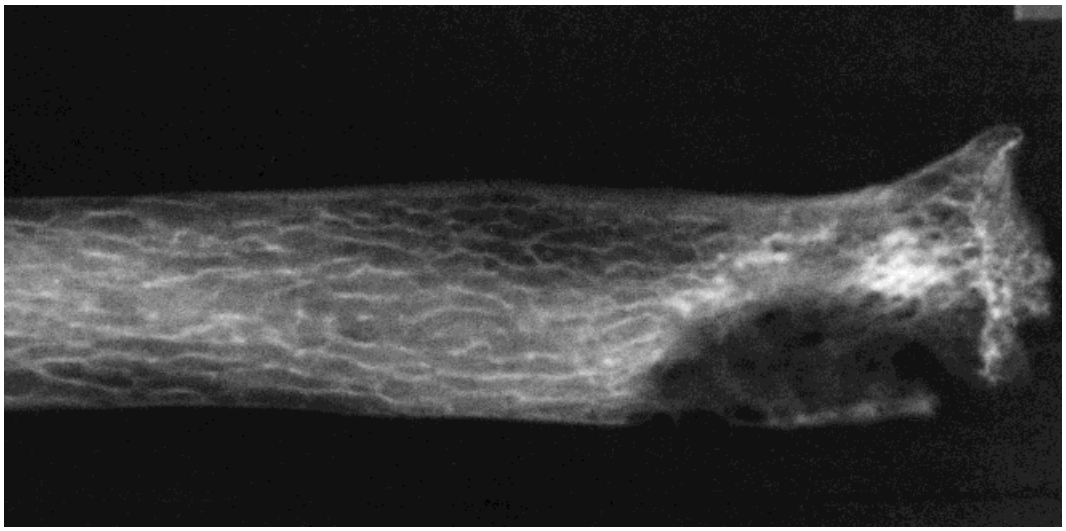

Fig. 8. Anterior-posterior x-ray view of sternal end of rib (Terry 833R) illustrated in Fig. 7. A lytic lesion with minimal sclerosis. In addition to generalized osteopenia, a moth-eaten, Swiss-cheese-like pattern is present.

Turner, 1970; Barrack et al., 1983; Bayer et al., 1979; Bayer and Guze, 1978, 1979; Bjorksten and Boquist, 1980; Bried and Galgiani, 1986; Buikstra, 1976; Carter, 1934; Chleboun and Nade, 1977; Colonna and Gucker, 1944; Dalinka and Greendyke, 1971; de Dios Colmenero et al., 1991; El-Najjar, 1981; Gehweiler et al., 1970; Goodwin et al., 1980;

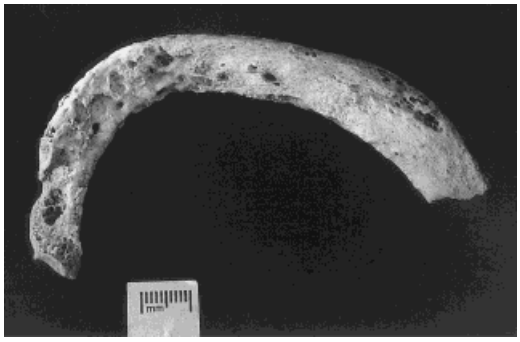

Fig. 9. Inferior aspect of rib from an individual with tuberculosis (HTH-1480). Note smooth zones of resorption.

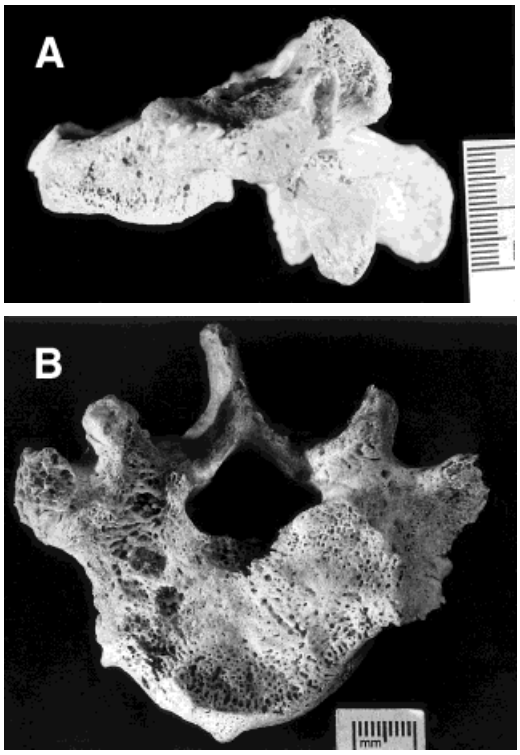

Fig. 10. Lumbar vertebra from an individual with tuberculosis (HTH-1204). **A:** Lateral view. **B:** Superior view. A collapse producing vertebra plana. Note zones of resorption in superior view.

Jones and Martin, 1941; Kalbhen, 1991; MacDonald et al., 1990; Nicholson, 1974; Rao et al., 1991; Rothschild and Rothschild, 1995a; Torricelli et al., 1990; Waldvogel et al., 1970). While concurrent diseases (e.g., AIDS) are known to alter the intensity of infectious/neoplastic disease, there appears to be no evidence that they actually alter the lesions. Thus, a valid diagnostic approach seems possible.

Differential diagnosis (Tables 1–3)

The major fungal infections of bone are histoplasmosis, coccidioidomycosis, cryptococcosis, blastomycosis, and candidiasis (Ortner and Putschar, 1981; Resnick and Niwayama, 1988; Rothschild and Martin, 1993). In addition to these fungal infections, differential diagnosis of blastomycosis includes tuberculosis, syphilis, brucellosis, echinococcus, metastatic cancer, and primary bone tumors. Sarcoidosis, while also a granulomatous disease, does not appear to be in the differential diagnosis because of the rather unique radiologic nature of the bone lesions it produces: cystic metaphyseal radiolucencies and diaphyseal cortex obliteration in the hands and feet and honeycomb or cyst-like structures with sclerotic margins (Buikstra, 1976; Resnick and Niwayama, 1988). These are apparently not observed in blastomycosis. The appearance of sarcoidosis in defleshed bone is unknown.

Tuberculosis is predominantly a disease of joints (El-Najjar, 1981; Nicholson, 1974; Resnick and Niwayama, 1988). Nonarticular involvement is usually diaphyseal in distribution (with exception of tibia), in contrast to metaphyseal and calvarial distribution in blastomycosis (Resnick and Niwayama, 1988). Vertebral involvement in tuberculosis predominantly affects the vertebral body, largely sparing posterior elements, in contrast to blastomycosis (Gehweiler et al., 1970; Resnick and Niwayama, 1988). Smooth, macroscopic zones of resorption (Fig. 11) appear to be the most characteristic aspect of lytic lesions in tuberculosis. This regional resorption is quite different in appearance and probably pathophysiology from the small foci (Figs. 1, 10) that make up the fronts of resorption seen in blastomycosis. It could be hypothesized that caseating granulomas, which some consider pathognomonic for tuberculosis (Harrison et al., 1991), are responsible for this apparently unique zone-of-resorption pattern.

Gummatous lesions of treponemal disease (Rothschild and Heathcote, 1993) are quite

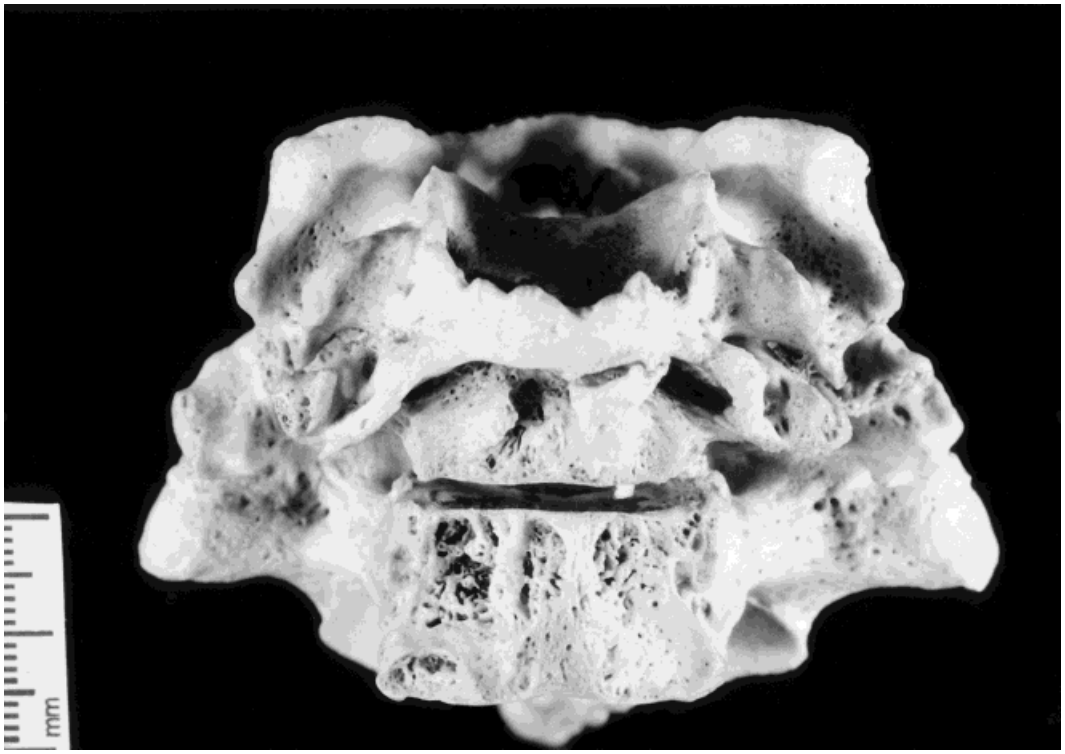

Fig. 11. Anterior view of cervical and first thoracic vertebrae from an individual with tuberculosis (HTH-1493). Destruction of the body of the fifth through seventh cervical vertebrae is extensive, leaving only residual remodeling external rings of the fifth and seventh as vestiges of the original vertebral body. The sixth vertebral body is totally destroyed, while posterior elements are spared. The result is a classic gibbus deformity. New bone formation is quite modest. Space-occupying lesions (draining abscesses) are associated with smoothing of subjacent vertebrae, as a result of new bone formation-induced remodeling.

different in appearance than those observed in blastomycosis and are associated with generalized bone sclerosis (Goff, 1967; Hackett, 1963; Jostes and Roche, 1939; Resnick and Niwayama, 1988; Rothschild and Martin, 1993; Rothschild and Rothschild, 1995b; Steinbach, 1966; Steinbock, 1976). The spiculated and multilaminated periosteal reaction of syphilis also does not occur in blastomycosis.

The other major granulomatous disorders are brucellosis and echinococcus. Brucellosis predominantly affects vertebrae while sparing other bones (Buikstra, 1976; de Dios Colmenero et al., 1991; Resnick and Niwayama, 1988). Echinococcus spares the skull and sternum (Buikstra, 1976; Rao et al., 1991; Resnick and Niwayama, 1988; Rothschild and Martin, 1993; Torricelli et al., 1990). Granulomatous reaction to the cysts in echinococcus resulted in its classification as a granulomatous disorder (Rao et al., 1991). The osseous impact of brucellosis and echinococcus, however, has not yet been sufficiently characterized in defleshed bones to allow further comment on differential considerations.

Permeative lesions of metastatic cancer are easily distinguished from areas of lysis, characteristic of blastomycosis. Discrete lytic lesions in individuals with metastatic cancer (Fig. 14) have a space-occupying appearance, distinct from the fronts of resorption noted in blastomycosis (Rothschild and Martin, 1993; Rothschild and Rothschild, 1995a). The blunt spicules present in blastomycosis are notably absent in metastatic cancer.

The lesions of blastomycosis are easily distinguished from the expansile, soap-bubble appearance of aneurysmal bone cysts,

Fig. 12. Posterior aspect of sacrum from an individual with metastatic cancer (HTH-788). A discrete lytic lesion has a space-occupied appearance—an expansile bone-displacing mass. No evidence of cortical remodeling.

trans-metaphyseal unicameral bone cysts, the radiolucent nidus of osteoid osteoma, the large lytic metaphyseal lesions of osteoblastomas, the epiphyseal "popcorn" calcifications characteristic of chondroblastomas, the diaphyseal distribution of enchondromas, the eccentric long bone lesions of chondromyxoid fibromas, the ground-glass appearance of fibrous dysplasia, the onion skin periosteal reaction and ill-defined margins of Ewing sarcoma and osteosarcoma, and the space-occupying mass appearance of eosinophilic granuloma (Resnick and Niwayama, 1988; Zias, 1996).

Additional verification

An additional source of confirmation of diagnostic specificity of findings appears reasonable to share. One of the authors (B.M.R.) was initially shown T-833R without any diagnostic information. He recognized it as different from what he had previously seen

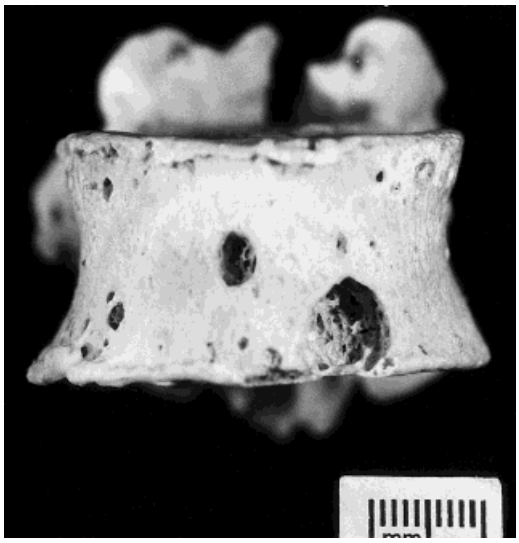

Fig. 13. Anterior view of thoracic vertebrae from an individual with metastatic cancer (HTH-788). A discrete lytic lesion has a space-occupied appearance with no evidence of cortical remodeling.

Fig. 14. Anterolateral view of second cervical vertebra from individual with metastatic cancer (HTH-2147). Empty deep cavity surrounded by residual cortical bone (the shell).

in cancer and tuberculosis. The presence of periosteal reaction led him a priori to suspect fungal disease, and the derivation of the Terry Collection from St. Louis led him to suspect blastomycosis.

One of us (B.M.R.) also examined cases of diagnosed coccidioidomycosis in primates and dogs to assess the specificity of findings for fungal disease. The findings were identical to those seen in this case of blastomycosis. Those cases will be reviewed by Chuck Merbs and Mike Schultz in their forthcoming manuscript.

Denouement

It would appear that metastatic cancer, tuberculosis, and fungal disease can be distinguished. Our initial assessment was that the lesions in T-833R were different in character than those previously observed in skeletons of individuals with clinically documented tuberculosis or cancer. Critical analysis documented those osseous alterations to be distinguishable from lesions of tuberculosis and metastatic cancer. Further observations on osseous lesions from individuals with other clinically established diagnoses are required to establish full diagnostic specificity.

ACKNOWLEDGMENTS

We thank Dr. Donald Ortner and Ms. Agnes Stix for their support and assistance in examination of the Terry Collection. This research was carried out during the sabbatical of one of us (I.H.) at the Cleveland Museum of Natural History. It is part of collaborative research project entitled Dynamic Patterns in Human Skeletal Biology among the following: la Laboratoire d'Anthropologie Biologique, Faculte de Medecine de Marseille, Universite de la Mediterranee, France; The Arthritis Center of Northeast Ohio, Youngstown, Ohio; Department of Physical Anthropology, Cleveland Museum of Natural History and Department of Anatomy, Case Western University, Cleveland, Ohio; and Department of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel Aviv University, Israel. This research was supported in part by a grant from the National Museum of Natural History, Smithsonian Institution.

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